REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the above amendment. The attached pages begin with the caption "**Version with markings to show changes made.**"

Claims 3 and 30-48 were pending in the present application. Applicants have amended claim 3 for reasons related to business considerations and to tailor the claims to currently contemplated embodiments of the invention rather than in acquiescence to any reason related to patentability. Specifically, limitations from claims 32, 33 and claim 3 as previously presented in Paper No. 8 (Response filed June 1, 2001) have been introduced into claim 3. Claims 30 and 31 have been canceled without prejudice.

Claim 34 has been amended to correct its dependency. Claim 36 has been amended to clarify the intended scope, and claim 38 has been amended to correct a typographical error.

Claim 46 has been canceled in favor of new claims 49-51, which is conformed to amended claim 3. Support for these claims is provided at least on page 41, lines 7-17; and Figure 45d.

New claim 52 is directed to a preferred embodiment of the invention wherein the polyamine comprises an ornithine moiety and is supported at least in Figure 45f. New claim 53 is dependent from claim 37 and is supported at least by claims 37-39 as filed.

No new matter has been presented, and entry of the amendments is respectfully requested.

Allowable Subject Matter and Withdrawn Claims

Applicants thank the Examiner for noting that Applicants' elected species of compound 1158 is allowable and the extension of the search to compounds where RC(O) is valine or lysine (Office Action, page 2). However, the Examiner withdrew claims 35-48 as "not embracing the elected species and/or because they contained non-examined species" (Office Action, page 2). Applicants respectfully traverse the withdrawal of claims 35-45 and 47-48 (due to the cancellation of claim 46) from consideration.

As the Examiner is no doubt aware, dependent claims contain all of the limitations of the claims from which they depend. Contrary to the Examiner's assertion, withdrawn claims 35-45

and 47-48 do not exclude the elected species or the species to which the search has been extended. Because withdrawn claims 35-45 and 47-48 are dependent from examined claims and do not exclude the elected species, they may not be withdrawn from consideration because they **do** "embrace the elected species". To the extent that they may "contain non-examined species", Applicants note that the claims must still be examined to the extent that they encompass the elected species.

Therefore, Applicants respectfully request that withdrawn claims 35-45 and 47-48 be rejoined with claims 3, 33 and 34.

The Claims Are Enabled

The Examiner rejected claim 3 under 35 U.S.C. § 112, first paragraph. The Examiner asserts that claim 3 does not reasonably provide enablement for claims where R is a mono-substituent, but is enabling for compounds where R recites specific substituents as amended in Paper No. 8 (Office Action, page 2). To further the prosecution of the present invention and tailor the claims to currently contemplated embodiments of the invention, and without acquiescing to the Examiner's arguments, Applicants have amended claim 3. Applicants reserve the right to pursue subject matter no longer encompassed by amended claim 3 in the future. Additionally, Applicants have not surrendered claim scope between the language of claim 3 as amended and as previously presented.

Applicants address the Examiner's rejection in view of Applicants' amendments. As amended, claim 3 recites specific R substituents. The specification teaches how to make and use polyamine derivatives having the formula R-CO-NH-$(CH_2)_3$-NH-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2, wherein R is selected from the group consisting of a D or L amino acid, D or L ornithine, an alicyclic, an aromatic, and a heterocyclic. For example, Figure 2 describes examples of polyamine derivatives of the presently claimed invention, and their effects on cell growth. The compounds can be synthesized using conventional coupling methods known to one of ordinary skill in the art, such as coupling of amines to carbonyl groups. Thus, the amended claims are enabled, and Applicants respectfully request that this rejection be withdrawn.

The Claims Are Novel

The Examiner rejected claims 3 and 33 under 35 U.S.C. § 102(b), as allegedly being anticipated by "Gunthorpe *et al.* (Toxicon, vol. 28, No. 11)". No copy of the cited reference was provided, and Applicants have been unable to obtain a copy of the reference as cited. Applicants are aware of a reference Bruce *et al.* (Toxicon, vol. 28, no. 11, pp. 1333-1346, 1990) which has a Table 7. A copy of that reference was provided in an Information Disclosure Statement and was acknowledged by initials on a Form PTO-1449 provided with the instant Office Action. Therefore, Applicants will address the instant rejection in light of Bruce *et al.* The Examiner is requested to contact the undersigned immediately if some other reference by "Gunthorpe et al." is intended as the basis for the instant rejection.

The reference is alleged to disclose acylspermines in Table 7. Claim 3 has been amended to no longer encompass acylspermines. Claim 33, directed to compounds comprising a D or L amino acid or ornithine, does not encompass acylspermines and so cannot be anticipated by the cited reference. Applicants respectfully submit that the instant rejection has been obviated and may be properly withdrawn.

The Examiner also rejected claims 3, 33 and 34, as allegedly being anticipated by Cherksey *et al.* (WO 91/00853). In particular, the Examiner asserts that Cherksey *et al.* disclose lysylspermine on page 19 therein. Applicants respectfully traverse because no *prima facie* case of anticipation has been presented.

Claim 3 specifically excludes a compound represented by formula ID 1202, the structure of which is shown in Figure 45e as being the L- isomer of lysylspermine due to the chirality at the alpha carbon of the lysyl group. Claims 33 and 34 are dependent from claim 3 and so contain all the limitations of claim 3. Therefore, claims 3, 33 and 34 are directed to the D- isomer of lysylspermine. Cherksey *et al.* describe lysylspermine without indication of chirality and so **they do not teach the D- isomer**. In the absence of an express teaching of the D- isomer, Cherksey *et al.* cannot, as a matter of law, anticipate claims 3, 33 and 34.

To the extent that the instant rejection may be based upon an interpretation that Cherksey *et al.* teach a racemic mixture of the D- and L- isomers of lysylspermine, Applicants respectfully point out that it is settled law that disclosure of a racemate (*i.e.*, combination of D and L isomers) does not anticipate claims directed to only one isomer. "[N]ovelty of an optical isomer is not

negated by prior art disclosure of its racemate" *In re May and Eddy* 197 U.S.P.Q. 601, 607 (CCPA 1978) (quoting *In re Williams*, 171 F.2d 319, 80 (CCPA 1948)). If Cherksey *et al.* describe racemic lysylspermines, claims 36-41, and 44 are not anticipated as a matter of law. Therefore, Applicants respectfully request that this rejection be withdrawn because no *prima facie* case of anticipation has been presented.

The Claims Are Non-Obvious

The Examiner rejected claims 3, 30 and 31 under 35 U.S.C. § 103(a), as allegedly being unpatentable under "Gunthorpe *et al.*" and *In re Mills*. As noted above, Applicants have not been able to locate the cited reference and therefore address the Examiner's arguments in view of Bruce *et al.*

Claim 3 has been amended to no longer encompass acylspermines, and claims 30 and 31 have been canceled. Applicants note that *In re Mills* is discussed as part of the standards set forth at MPEP 2144.09. Those standards require that an allegation of obviousness based on structural similarities be based upon compounds with "very close structural similarities and similar utilities". In the instant case, the claims no longer encompass compounds with "very close structural similarities" to the acylspermines in Table 7 of the cited reference.

Additionally, the present invention is directed to the use of the claimed compounds to inhibit polyamine transport and/or the inhibition of cell proliferation, which are properties not taught or suggested by the cited reference with respect to acylspermines. As such, the claimed compounds already display unexpected results over the acylspermines taught by the cited reference. Such unexpected results are sufficient to prevent the establishment of a *prima facie* case of obviousness as also noted in MPEP 2144.09.

Therefore, Applicants respectfully submit that the instant rejection may be properly withdrawn.

The Examiner also rejected claims 3, 30 and 31 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Cherksey *et al.* and *In re Mills*. The Examiner concedes that the homologues and pharmaceutical forms of the presently claimed invention differ from those compounds described in Cherksey *et al.* However, the Examiner asserts that it would have been

prima facie obvious "to start with the teaching of the cited reference to make positions isomers/homologues thereof and to expect them to be useful as P-channel activators" (Office Action, page 4). Applicants respectfully traverse because no *prima facie* case of obviousness has been presented.

As an initial matter, claims 30 and 31 have been canceled without prejudice.

Moreover, the asserted expectation of producing useful P-channel activators is speculative. This follows because Cherksey et al. describe the lysylspermine compound to be a *potential* P-channel activator (see page 19, lines 17-20). As such, any "obvious" isomers/homologues of the lysylspermine would at most be expected to be *potential* P-channel activators. Clearly, this amounts to an impermissible assertion of "obvious to try" to obtain additional P-channel activators by producing isomer/homologue compounds that *potentially* have such activity. Applicants respectfully submit that this is insufficient to support a *prima facie* case of obviousness.

Additionally, the present invention is directed to the use of the claimed compounds to inhibit polyamine transport and/or the inhibition of cell proliferation, which are properties not taught or suggested by Cherksey *et al.* As such, the claimed compounds already display unexpected results over the *potential* P-channel activating compound ("CC") taught by Cherksey *et al.* Such unexpected results are sufficient to prevent the establishment of a *prima facie* case of obviousness (see MPEP 2144.09).

To the extent that the instant rejection is based upon an alleged obviousness of position isomers and homologues of the single lysylspermine taught by Cherksey *et al.*, Applicants respectfully submit that even the D- isomer (or form) of lysylspermine possesses unexpected properties sufficient to render it non-obvious over the L- isomer.

As indicated in the attached Declaration of Dr. Reitha Weeks ("Weeks Declaration") submitted in related application 09/713,512, the D- form of lysylspermine showed unexpected differences in tissue accumulation in comparison to the L-form of lysylspermine. In particular, the tissue concentrations of the L- and D- forms of lysylspermine when measured from mouse liver, kidney and heart tissues, are significantly different after 13 days. (Weeks Declaration, ¶¶ 6 and 7). Specifically, the concentrations of the D- form were unexpectedly higher than that of the L- form. The higher tissue concentration of the D- form of lysylspermine has significance for the use of the compound in the inhibition of polyamine transport and/or the inhibition of cell

proliferation. Higher tissue concentrations permit the use of lower amounts of a compound to achieve the same biological effect, such as polyamine transport inhibition and/or inhibition of cell proliferation, in a tissue.

In light of the unexpected differences in properties between D- and L- lysylspermine, Applicants respectfully submit that claim 3 is not obvious over Cherksey *et al.* Applicants respectfully request that this rejection be withdrawn.

Obviousness Double Patenting Rejection

The Examiner rejected claims 3, 30-31, and 33-34 under the doctrine of obviousness-type double patenting under the claims of U.S. Patent Application No. 09/713,512. The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they generically overlap" (Office Action, page 5).

Applicants respectfully note that this appears to be a *provisional* rejection since the claims of the other application have not yet been patented. Applicants therefore respectfully request that this rejection be held in abeyance until the claims are otherwise indicated as allowable.

CONCLUSION

Having addressed all of the rejections, Applicants respectfully submit that the claims may be indicated as allowable, and a notice to that effect is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants' petition for any required relief including extensions of time and authorized the Assistant Commissioner of

Patents to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 275102001021.

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Respectfully submitted,

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Version with markings to show changes made.

In the Claims:

Please amend the pending claims as follows:

3. (Thrice Amended) A N^1-monosubstituted polyamine analogue or derivative represented by the formula

$$R\text{-}CO\text{-}NH\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH\text{-}(CH_2)_3\text{-}NH_2$$

wherein R is selected from a D or L amino acid; D or L ornithine, an alicyclic, a single or multi-ring aromatic; aliphatic-substituted single or multi-ring aromatic; and a substituted or unsubstituted, single or multi-ring heterocyclic [~~represents a monosubstituent~~], and

wherein said analogue or derivative does not have a formula represented by ID 1022, 1043, [~~1085, 1107, 1111, 1163, 1166,~~] or 1202[~~, or 1260~~].

33.(amended) An analogue or derivative according to claim 3 wherein R is a D or L amino acid or D or L ornithine.

34.(amended) A composition comprising a polyamine analogue or derivative according to [any one of claims 3 or 30-33] claim 3, 32 or 33 and a pharmaceutically acceptable excipient.

38.(amended) A method according to claim 37 wherein said undesired cell proliferation is associated with proliferation of cells of the immune system, cells of the vascular neontima, tumor cells or with undesired angiogenesis.